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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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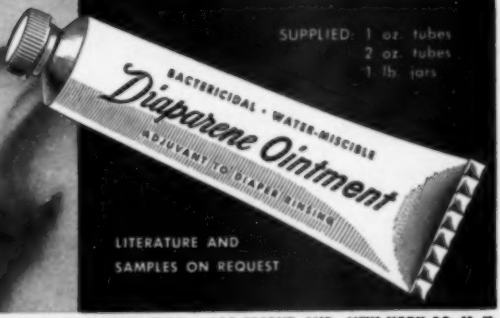

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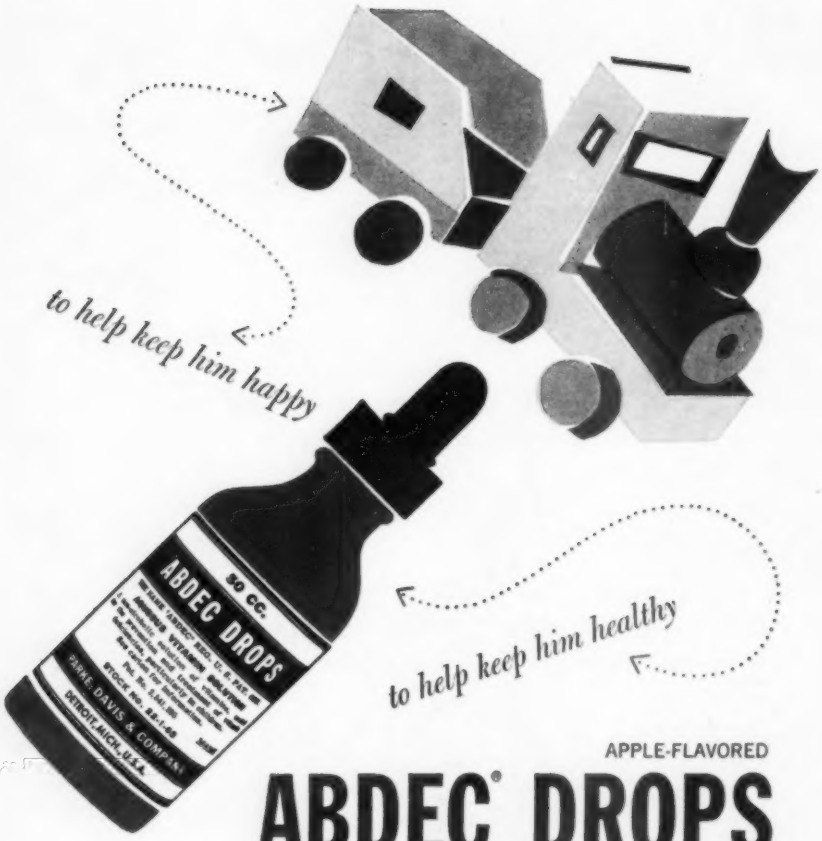

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THE TREATMENT OF MENTAL DEFICIENCY AND ENCEPHALOPATHIES IN CHILDHOOD BY MEANS OF FRESH TISSUE AND SICCACELL

GEORG DESTUNIS, M.D.*
Berlin, Germany.

In 1948 Niehans reported his treatment of Mongolism using cells of the thyroid and thymus. He later employed fresh cells from the frontal lobe of the brain for mental deficiency and brain injury in childhood; from time to time, he also gave cells from the basal ganglia and hypothalamus in combination with cells of the cerebral cortex. Encouraging results were achieved. For some years now Haubold[1] has been treating Mongolism with siccacells,[2] such as thymus, placenta, thyroid, pituitary, hypothalamus and cerebrum, in various combinations at intervals of six to twelve months. He gives vitamins and trace elements as supplements.

In 1952, in the Friedrichshain Hospital in Berlin, my coworker, Dr. Ernst Schmidt and I[4] began treating mental deficiency and encephalopathies from various causes. We called our type of treatment *diencephalon implantation* and reported our first results by this method at a meeting of the Neurological Society of Berlin in 1953. In 1956 we published our first observations and results in the "Medizinischen Klinik" under the title, "Diencephalon implantation for encephalopathies and mental deficiency from

* Professor at Berlin University, Berlin, Germany.

various causes in childhood." This paper reports our observations in 45 cases. In a paper read at the Therapy Congress in Karlsruhe in the same year, I reported results in a series of 92 cases. At the present time, the number of cases has risen to 113.

Technique of diencephalon implantation: The fact that our hospital is only five minutes distance from the main slaughter house enables us to obtain freshly slaughtered calves' heads with the shortest possible delay. These animals are previously examined by the veterinary surgeon of the slaughter house, so that the possibility of transmission of a zoonosis can be excluded with certainty. The brain is removed from the skull under sterile precautions and a piece of brain is excised, comprising the whole diencephalon and weighing roughly 20 gm. (without pituitary). The dose can be increased in certain cases by taking a piece of hypothalamus from another brain, but not more than 10 gm. additional brain substance. The tissue is comminuted into pieces with a side measurement of 1 mm. by means of scissors and stirred with the same scissors into a kind of mash to which we add 6 ml. saline solution and 100,000 to 200,000 units of penicillin, depending on the age of the child. The whole mixture is drawn into a 20 ml. syringe and injected intramuscularly through a wide bore cannula into the gluteal region under strong pressure. In small children, we inject half of the brain mash into the right side and the other half into the left, without previous infiltration with novocaine. The speed which the injection is made ensures that the injection is relatively painless. If necessary, we repeat the implantation eight to ten weeks later, and possibly a third time after a similar interval.

We once gave a child a fourth implantation, one year after the previous one; the injection was badly tolerated, the child reacting with severe vomiting, which normally does not occur. For this reason we do not give more than three injections in a period of nine months to two years.

Preparatory testing: Since there is risk of anaphylaxis or allergy when injecting such large quantities of brain substance, we carry out a test one week prior to implantation, to exclude the possibility of an anaphylactic or allergic diathesis. The technique is as follows: Several milliliters of finely comminuted calves diencephalon are mixed with a similar quantity of physiological saline solution. This mixture is centrifuged for forty minutes at 3000 r.p.m. The

supernatant fluid is decanted and injected intracutaneously. Thirty minutes later the skin is examined; if there is no reaction, a subcutaneous injection is made. The skin is again examined thirty minutes later, and in doubtful cases, 3 ml. is injected intramuscularly.

The test is considered positive if a specific local reaction occurs with a sharply defined circumscribed erythema, about 4 cm. in diameter (test for allergy). Since in some cases the reaction only developed after eight days (anaphylaxis), we only carried out the implantation a week after the test.

The indications for implantation: We have employed this method for the following conditions:

1. Mental deficiency of endogenous origin.
2. Encephalopathies (infantile cerebral palsy from various causes, and following encephalitis, birth injury, Little's disease, immaturity, RH factors, etc.).
3. Mental retardation from various causes.
4. Mongoloid idiocy.
5. Pituitary insufficiency (mild pituitary cachexia).

Whereas in mental deficiency we exclude extremely retarded mental defectives, we carry out implantation in encephalopathies, in severe cases as well as mild ones, because we have found empirically that spasm and stiffness as well as other extrapyramidal phenomena can be alleviated, which is a relief to the patients.

Results of diencephalon implantation in mental deficiency and encephalopathies: After the stress phase due to the implantation, lasting in children from two to three days (local swelling, possibly erythema, subfebrile temperatures, restlessness and loss of appetite), *revitalization* follows; the children become more alert, fresher and more balanced. The appetite increases, sleep becomes deeper and more restful. Both the mood of the children and their interest in their surroundings improve. They give the impression that they have just returned from a holiday.

SPECIAL EFFECTS

Impulsion: The drive increases, the children take a more active part in the daily life of the family and at school. They show more interest in school work.

Intelligence: In general among the children treated, intelligence advanced by six to twelve months. Memory and capacity for attention particularly improved.

Speech: The function of speech also improves. The child learns new words and forms new sentences, or begins to form sentences, (e.g., in Mongolism, where speech development is very retarded). There is no time limit on the improvement, and it may continue for several years after implantation.

Motor system: Motor development is promoted; children unable to walk because of delayed motor development, usually begin to walk some weeks after implantation. Prehension improves, and the child's skill increases. The gait, ungainly, uncertain and straddle-legged in Mongoloids, and spastic or cerebellar in encephalopathy, improves becoming steady and easier.

Tonus: We were surprised to see that in many children with cerebral injury and spastic phenomena (including Little's disease) the spasm became less intense and the spastic gait improved.

Extrapyramidal symptoms: These improved after diencephalon implantation, athetoid movements became less or disappeared.

Epileptic fits: These are more frequent perhaps two to three weeks after implantation, but disappear later, or become rare.

Body growth: It is particularly interesting to note that the children grow more rapidly after diencephalon implantation, especially if it is carried out prior to puberty. We have seen some extreme cases where the child has grown 10 to 15 cm. in the year the implantation was done.

We found diencephalon implantation more successful when the children were under the age of six. We presume that a brain which is not yet differentiated responds better to the biological impulse afforded by implantation. It is known that by the sixth year the brain has completed a certain degree of development.

We give below a table of the 113 cases of implantation, arranged according to disease and treatment results.

	Total	Improved	Unchanged
1. Encephalopathies	44	37	7
2. Mongoloid idiocy	30	24	6
3. Borderline mental deficiency	17	15	2

4. High grade mental deficiency (of various causes, both endogenous and exogenous)	12	10	2
5. Developmental disorders of speech and motor system	4	1	3
6. Pituitary disorders (insufficiency)	6	3	3
	113	90	23

We have been observing the after effects of diencephalon implantation over a period of five years. We can state definitely that a late effect can also be expected, usually in the form of good physical development and better growth. There is in addition the possibility of late endocrine effects; in our series of one hundred and thirteen cases we had one case of adipose gigantism, one case of Mongoloid adiposis and two acromegaloids. Diencephalon implantation had been carried out either prior to, or during puberty. The case of adipose gigantism gained 23 kg. in weight and grew 22 cm. in three years, the diencephalon implantation being done in 1953 when he was 11 years old. He has become a good student although before implantation he had twice failed his examinations.

Since 1956,[5] the siccacell preparations manufactured by the process of lyophilization have become available. Since then we have attempted to check the effects of these cells against our own method of diencephalon implantation, and to work out a dosage scheme, adapted to the degree of severity of the disease and the age of the patient. We have not yet had much experience with these preparations, but we can state in general that results are satisfactory. In ten cases of mental deficiency of various causes (hereditary, and exogenous, but not mongoloid), we made one or two injections of siccacell hypothalamus and frontal brain in patients, aged two to twelve years at intervals of six to eight weeks. The main advantage of these injections is that they are well tolerated. They are not at all painful and give rise to no local reaction (erythema or swelling). A further advantage is the absence of allergic or anaphylactic reactions, particularly with embryonic siccacell. Procuring material from the slaughter house and the complex procedure of fresh cell therapy become unnecessary when siccacell is used. The stress phase, lasting two to three days, is

very brief, and, compared to that of diencephalon implantation, very mild or even completely absent.

Three cases of mental deficiency associated with dwarfism were treated simultaneously with one ampoule of hypothalamus and two ampoules of anterior lobe pituitary. The injections were very well tolerated. In two other cases, I gave two injections of hypothalamus, also without any local or general reaction.

I treated three cases of myxedema aged six to fourteen years with siccacell thyroid at six week intervals, after discontinuing the thyreoidin which the children had been taking for several years. As long as the effect of cellular therapy persisted, the children were vivacious and felt well. To date, I have given three injections, in each case at intervals of six weeks. Further research in this field is required.

These are the first trials of this kind that we have made, and they are of a tentative nature. The general impression, from this small series of cases, is that siccacell therapy yields similar results to those of diencephalon implantation. The children become vitalized, more vivacious, more attentive, have more endurance in play, and are more reasonable in their behaviour. Speech development is promoted, speaking becomes easier, sentence formation improves, the body, in general, develops better. Diencephalon implantation is also known to have all these effects. We cannot as yet say anything conclusive about the comparative efficacy of these two forms of cellular therapy owing to the short period of observation (six months); this is also too short for anything definite to be said as to the lasting effects of siccacell therapy. However, in my opinion the intervals between injections should be shortened to six weeks, the injections being repeated at least three times in order to provide the brain, which has suffered early damage in childhood, with the impulse to further development.

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HYPO- AND HYPERTHYROIDISM IN MONGOLISM

FATMA MUNIRE ESEN, M.D.
and
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Mongolism is in many respects an unsolved riddle. The role of the endocrine glands in this disease is a much discussed chapter. The function of the thyroid as well as the pituary gland has been of special interest. Bourneville[1] was probably the first to describe pathological changes in the thyroid gland; Gordon[2] and Pennacchietti[3] also found abnormal thyroids in mongoloids. The detailed studies of Benda[4] have confirmed that the thyroid glands of mongoloids are nearly always underdeveloped, and often combined with colloid retention. Recently, Freedberg, Hamolski and Freedberg[5] who have reviewed the role of the thyroid in pregnancy and in mongolism report the following data: Lowry[6] and coworkers found lower 24^h uptake of iodine in a one month old mongoloid; but Kearns and Hutson,[7] Simon[8] and coworkers, and McGirr[9] could not confirm these findings. Friedman[10] could not find differences in the radioiodine uptake of mongoloids or of normal children. Neither have Freedberg and coworkers seen significant abnormalities in the 24^h uptake, plasma iodine conversion ratios or serum protein-bound iodine level urinary excretion of iodine. On the other hand, the thyroid glands of mongoloid subjects showed a significantly faster effective half life or decrease in radioactivity than those of an euthyroid control group. Furthermore, a possible abnormality of the plasma-protein-thyroid-hormone complex in mongolism was suggested by an increase in vitro red cell uptake of iodine labeled tri-iodo-thyronine from whole blood. The role of the thyroid gland in mongolism is, therefore, not fully understood, but it seems that in general, while the gland is rather underdeveloped, it is able to react to the pituitary thyroid stimulating hormone. The thyroid hormone reaches the circulation slowly so that colloid tends to accumulate. Mild degrees of hypofunction of the thyroid are not rare in mongoloids. Hyperfunction has also been observed. Such mongoloids with thyrotoxic symptoms have been described by Pennacchieti, McGirr and others.

* Dr. Esen, in the early Fall, will leave for Ankara, Turkey where he will be affiliated with the Children's Hospital.

In this state of limited knowledge, it seems worthwhile to report on two patients under our observation who represent the two extreme possibilities of thyroid activity: a cretinic and thyrotoxic mongoloid.

Case 1. A.M.C., white female, was delivered at term at the Worcester City Hospital on October 17, 1941, by low forceps delivery. Birth weight was 2700 grams. The mother was 19 years of age and this was her first pregnancy. There were no siblings. Some signs of mongolism were observed, such as a large tongue, slanting eyes, overstretched joints, but the diagnosis seemed rather questionable. In 1944, the patient was seen at the Out-Patient Clinic of the Walter Fernald School where the definite diagnosis of mongolism was made. Fig. 1).

Fig. 1. Case 1. At 3 years of age with mongoloid appearance.

Fig. 2. Case 1. At 7 years of age with typical cretinoid appearance.

At the time her I.Q. was .57. She started to walk at the age of 16 months, and to talk at 3 years. She was admitted to Wrentham State School at 7 years of age (November 23, 1948). She appeared to be a typical cretin (Fig. 2). *Physical examination* revealed a stocky, obese white girl with epicanthal folds, slanting eyes, a convergent strabismus, a small nose, pathological ears strongly bent with thick, small helices. The little fingers were normal, four finger line across the palms, the extremities short, the abdomen protruding. The heart has not shown any pathological signs clinically, nor in x-ray pictures. The thyroid was not palpable. Her mental development was that of a child of 2 years and 2 months, giving her an I.Q. of .31. Bone age was mildly retarded.

The laboratory findings: Hemoglobin 9.5 gm. per cent; RBC: 3,600,000; WBC: 8,900; Hinton test negative. She was given large doses of thyroid, four grains daily for 3 weeks, at which time she developed a tachycardia; treatment was stopped. Three days later treatment was reinstituted with a half grain daily, but soon increased to one-quarter grain three times daily. She became very active, lost weight and her appearance that of a typical mongoloid. (Fig. 3). Her treatment was inadvertently discontinued in 1954, when she was under the care of another physician; again she developed signs of hypothyroidism, including myxedema and deteriorated mentally. It was not until June 1956 that thyroid was again administered. Following a dose of one-quarter grain of desiccated thyroid three times daily she again improved, but more slowly than before.

Fig. 3. Case 1. At 12 years of age, after treatment, with typical mongoloid features.

The cholesterol values were:	in 1948	289 mgm%
	in 1949	228 mgm%
	in 1953	216 mgm%
	in July 1956	330 mgm%
	in Aug. 1956	325 mgm%
	in Oct. 1956	208 mgm%

These figures show that the cholesterol level was not excessively high at admission, and decreased during treatment, then increased considerably when treatment was stopped, but could be brought down to normal levels by repeated thyroid therapy.

At present, (Fig. 4), she weighs 48,600 grams and is 137 cm. tall. The dosage of thyroid intake was increased to one grain daily which she has been receiving up to the time of this writing. She is tidy, well behaved; likes to help dress younger children. She attends Sense Training Classes and movies, enjoys listening to radio or watching television. She says a few words only. Menarche occurred in 1956.

Fig. 4. Case 1. At 16 years of age, after discontinuance of treatment, with milder cretinoid appearance.

In summary, we are concerned with a mongoloid girl who at the age of about 6 years developed severe hypofunction of the thyroid gland with signs and symptoms of cretinism. Treatment with desiccated thyroid changed her features and she became more alert, less obese and appeared as a typical mongoloid. When treatment was stopped the cretinoid features reappeared. Re-established thyroid treatment resulted in some improvement in her lethargy and myxedema, but the general appearance of cretinism has not completely disappeared.

Case 2. J.L., white mongoloid female, born July 26, 1940, by premature and instrumental delivery at eight months, because of mother's toxemia, (pre-eclampsia). Birth weight was 2013 grams. Mother was 43 years of age at birth of patient, and this was her fourth pregnancy. The prenatal course was complicated by several episodes of bleeding. The first pregnancy resulted in an

induced delivery at six and a half months because of toxemia, (pre-eclampsia) of the mother, and the baby lived eight hours. The results of the second pregnancy was a normal, intelligent girl who is married at present and has a normal baby. The third pregnancy resulted in a miscarriage at three months attributed to the mother's lifting a heavy pail of water. This miscarriage happened one year before our patient's birth. The mother stated that she was not properly cared for after the miscarriage. The parents are of normal intelligence. The baby was examined at the Boston City Hospital soon after birth and a diagnosis of "mongolism with congenital heart disease" was made. Dentition began at thirteen months; she walked at sixteen months and started to talk at twenty months of age.

The patient was admitted to the Wrentham State School on August 29, 1942 at the age of two years, one month. At that time, the *physical examination* revealed a blonde mongoloid girl who weighed 11 kg., and was 74 cm. tall. She had dark blue eyes with heterochromic irises, epicanthal folds, small nose with broad nasal bridge, small ears with very small ear canals and scarred drums, chapped chin and cheeks, mottled cyanosis of skin, harsh breathing sounds, a moderate sinus arhythmia, four finger (simian) line across the palms, a large fissured tongue, slanting eyes, narrow palate and a mild scoliosis of the lower dorsal spine. The head measured 46 cm. in circumference, 11½ cm. in width, and 14½ cm. in length.

In 1949, a fluoroscopic examination was made by Dr. Elkin. His report was as follows: "Examination of the heart by PA film and fluoroscopy shows the heart to be enlarged, measuring 10.6 cm. in transverse diameter with transthoracic measurement of 19.6 cm. In the PA picture, the heart appears enlarged generally but at fluoroscopy the enlargement appeared to be chiefly in the region of the right ventricle as well as auricular enlargement most likely in the right auricle. The right hilar shadows appear prominent, apparently due to engorged vessels, although no hilar density could be demonstrated. Impression: The appearance is that of a shunt from left to right such as an interauricular septal defect."

An ECG was taken. Dr. Luisada's report was as follows: "ECG: severe right axis deviation. Sinus rhythm. P-R-0.20. Phonocardiogram: Systolic murmur".

The *psychological examination* on admission revealed a mental age of 2 years and an I.Q. of .50. A more recent test, at 12 years of age, revealed a mental age of 2 years, 8 months and an I.Q. of .22.

Laboratory examinations. Hemoglobin: 11.4 gm. per cent; RBC: 4,500,000; WBC: 4,100 with 76 per cent polymorphonuclears: 18 per cent lymphocytes, 5 per cent monoctytes. The sedimentation rate was 56 mm. at the end of one hour. Total serum cholesterol was 152 m. per cent; normal urinanalysis. Hinton test was negative.

Course: The patient had a good disposition, ate and slept well, was tidy with clothing and in personal habits; played and got along well with other children. She attended Sense Training Class and entertainments. In spite of the congenital heart malformation, the patient's health was good in general until recent years, at which time she began to have frequent attacks of upper respiratory infections with tonsillitis. In August 1955 she developed exophthalmos, and at the same time weight loss and diarrhea were noticed. She had complained of headaches and had vomited in spite of good appetite, perspired moderately, especially of both palms. A roentgenogram of the chest on February 13, 1956 showed a slight deviation of the trachea which suggested enlarged thyroid on the right side. The basal metabolic test on February 16, 1956 showed a rate of plus 27 per cent. The pulse varied from 75 to 130 per minute. The weights were as follows: October 1955, 36 kg.; November 1955, 35 kg.; December 1955, 34 kg.; January 1956, 33 kg.; February 1956, 31 kg.

On March 12, 1956, the patient had pneumonia and in spite of extensive antibiotic treatment, temperature went up to 104°, pulse to 105°, respiration 68, she became cyanotic and died on March 17, 1956 at the age of 15 years, 7 months and 20 days.

Necropsy findings: The body measured 158 cm. in length and weighed 31 kg. Subcutaneous fat was 2 mm. deep in the chest and abdomen. The abdominal rectus muscle showed moderate atrophy and pallor. The cut surface of the breasts revealed cystic degeneration. During incision of the breast tissue a light yellowish mucus-like fluid flowed freely. Each pleural cavity contained 100 cc. of blood-tinged purulent exudate. The right lung weighed 463 gms. and the left 406 gms. There were confluent and scattered

partially hemorrhagic consolidated foci in the parenchyma of the right lung. The lingula showed marked elongation and curving. There was diffuse pneumonic consolidation of the entire left lower lobe (lobar pneumonia). The intervening lung parenchyma was markedly congested and yielded a large amount of blood-tinged frothy fluid under moderate pressure. Both pleural surfaces were covered with a greenish yellow purulent exudate, more extensive on the left. The thymus weighed 18 gms. The cut surface showed a pinkish gray glandular tissue. The thyroid was grossly enlarged, weighed 39 gms. and had a beefy consistency with moderate right lobe hyperplasia. Its external surface was smooth. The cut surface was rather pale and resembled the pancreas in texture. Here and there were a few yellowish-white circumscribed foci. The heart* was hypertrophic, weighing 200 gms. and showed a persistent ostium primum and patent foramen ovale.

The general configuration of the liver appeared normal, except for uniform reduction in size; it weighed 900 gms. The consistency of the liver was moderately increased. The capsule showed scattered opacity, but was thin and transparent in general, transmitting clearly the color of the underlying parenchyma. The usual architectural pattern of the cut surface was moderately altered by the fine nodules, marked congestion and fatty degeneration. The spleen weighed 220 gms. and was hyperplastic. The cut section revealed a bluish pink, soft parenchyma with hyperplasia of malpighian bodies. The splenic capsule showed a partially fibrous thickening especially in the hilus. There were a few enlarged, hyperemic lymph modes in the splenic hilus. The mesenteric and periaortic lymph nodes were markedly swollen and hyperemic. The pancreas weighed 60 gms. and grossly showed normal glandular structure. The kidneys weighed 100 gms. each and were markedly congested. The left adrenal gland weighed 6½ gms. and the right 5½ gms. The cortex of both adrenals showed marked decrease of lipoid content. The mucosa of the uterus revealed hyperemia with two lentil sized pendulous mucous polyps. There was almond sized paroophoric cysts on the left. Both ovaries revealed marked fibrosis with a hazelnut sized cyst on the left ovary. The lower portion of the spine showed moderate scoliosis. The bone marrow of the sternum and vertebral column was not remarkable. The

* Detailed autopsy finding of the heart are described in Dr. Esen's paper "Congenital heart malformation in mongoloids with special reference to the ostium atrioventriculare commune". ARCHIVES OF PEDIATRICS, Vol. 74, July 1957.

lymph nodes in general showed extraordinary swelling and hyperemia, especially in the paratracheal, perihilar, interpulmonary, intrapulmonary regions, and around the tracheal bifurcation. A few of the hilar lymph nodes showed marked softening. The brain weighed 1160 gms. and showed features usually found in older mongoloids, such as decrease in weight, flattened and broad convolutions, especially upon the convexity, compressed orbital gyri, hypoplasia of frontal poles with retroflexion, short temporal lobes with distorted temporal poles, fusion and distortion of the fissure, etc.

Microscopic examination. Several sections of the entire thyroid were made, which showed the same pattern in general. The

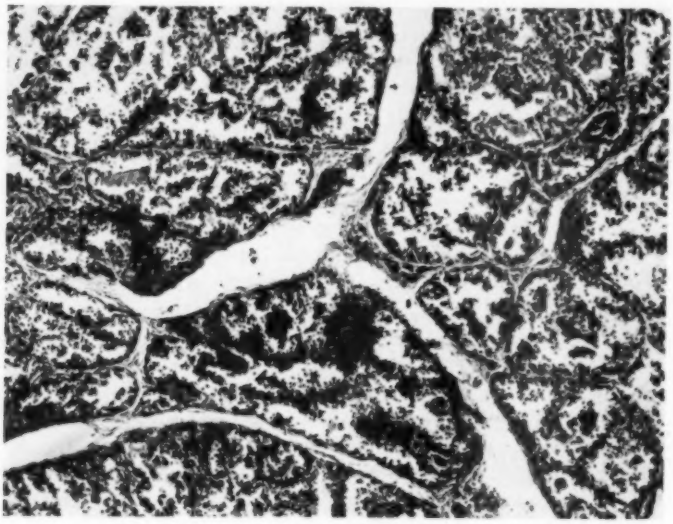

Fig. 5A. Case 2.

Photomicrograph. A low-power view of thyroid shows hyperplasia of acinar epithelium with marked decrease of colloid. Mag. X 150. Hematoxylin and eosin.

follicles were irregular in form and lined with tall columnar epithelial cells forming papillary proliferation with lace-like projections into the follicular lumina. The nuclei of the epithelial cells were closely packed and basal in position. There were scattered

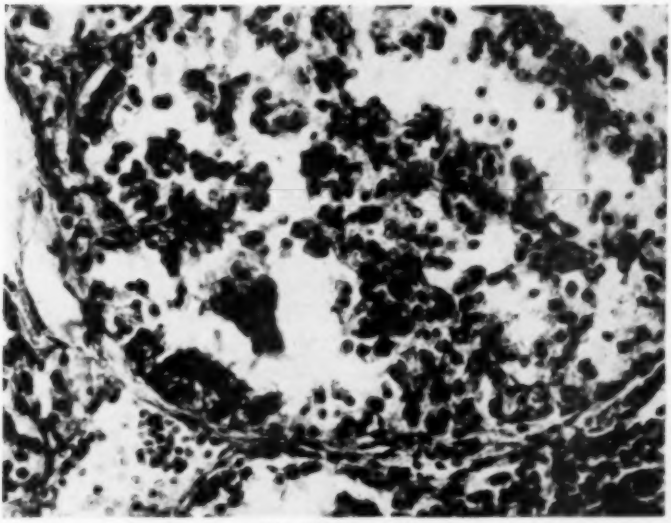

Fig. 5B. Case 2.
Photomicrograph. A high-power view of Fig. 5A shows hyperplasia of the acinar epithelium with intra acinar epithelial papillary projection and infoldings with absence of colloid in the acinar lumen. Mag. X 400. Hematoxylin and eosin.

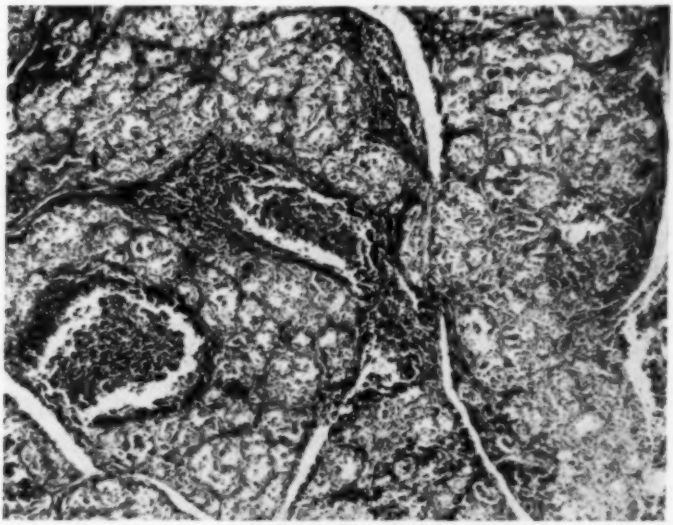

Fig. 6. Case 2.
Photomicrograph of thyroid. Note the accumulation of lymphocytes, some of which have distinct germinal centers. Mag. X 70. Hematoxylin and eosin.

mitotic figures throughout the sections. The colloid was markedly decreased in amount and almost completely disappeared in many areas (Figs. 5A and 5B). There were numerous new follicles with small lumina. The nodular structures represent increased limphoid tissue some of which had distinct germinal centers (Fig. 6). The thyroid gland was divided into lobules by bands of connective tissue. Degeneration of the heart muscle with patchy areas of necrosis and fibrous scarring was seen. Scar tissue was forming mostly around the capillaries and arterioles with a swollen endothelial lining. Scattered polymorphonuclear leukocytes, lymphocytes and monocytes in the connective tissue were apparent, especially in the perivascular region. Hypertrophy of muscle fibers was noticeable in places which showed enlarged round nuclei. There was a moderate increase in interstitial connective tissue in general. The hepatic cells showed marked disintegration with fatty metamorphosis, pyknotic changes and marked glycogenic vacuolization of nuclei so that the normal pattern was lost. There was an increase of periportal lymphatic infiltration and connective tissue. The irregular liver lobules were widely separated by fibrous tissue and some of them show degeneration, especially along the capsule. The spleen showed enlargement of the sinuses with proliferation of the sinus epithelial cells and connective tissue. There were scattered hemosiderin-laden microphages in the sinuses. The lymph nodes revealed marked hyperplasia of the lymphoid elements and dilatation of the lymphatic sinuses which were engorged with proliferated endothelial cells in most areas. The surrounding pulp was highly vascular. The histiocytic cells contained nuclear debris and were pervading the pulp. The thymus showed numerous, unusually large Hassall's corpuscles some of which had calcium deposits. The cortex and medulla were easily distinguished. There were numerous engorged capillaries. The cortex of the adrenal glands was narrow and rather hypoplastic. The lipoid was sparse and the cells and their arrangement were infantile in pattern especially in zona glomerulosa and zona fasiculata. Embedded in the capsule of the adrenal glands were a few spherical cortical nodules. The stroma showed increased vascularity. There were numerous islands of cortex present in the medulla. A moderate amount of diffused brown pigment was noticed in the cortex. The medulla showed a small amount of cellular infiltration which was composed of lymphocytes and polymorphonuclear leukocytes. The

breast showed cystic dilation of the mammary tubules with desquamated epithelium surrounded by increased amount of dense connective tissue. Some of the dilated ducts were lined with epithelium undergoing sweat gland metaplasia. The others were lined with a single layer of flattened cuboidal epithelium. Both adult hyalinized and young myxomatous connective tissue was present. Dr. Russfield was kind enough to examine the hypophysis and gave the following report: "The differential count on your case of untreated thyrotoxicosis (3400 cells from 97 fields) was as follows:

	Thyrotox	*Approx. Normal*
Normal basophils	2.3%	5–10%
Acidophils.....	34.3	35
Chromophobes	56.8	50
Amphophils	3.9	5
Hypertrophic amphophils ...	2.7	less than one

The only figure which seems definitely abnormal is the high percentage of hypertrophic amphophils. These are very large, bizarre, agranular cells which seem to correspond to the thyroidectomy cells of animals and which apparently increase in cases of an organ hyperactivity. The low normal values for basophils and amphophils are what we have seen in a few cases of thyrotoxicosis which had received Lugol's solution."

In summary, this mongoloid girl developed an acute thyrotoxicosis at the age of 15½ years, which was confirmed by the histological examination. The most impressive feature was marked hyperplasia of the acinar epithtelium of thyroid with intraacinar epithelial papillary infoldings, almost complete disappearance of colloid and scattered lymphoid accumulation throughout the gland. The histological findings of the cardiac muscle, liver, pituitary, lymph nodes, are similar to those described in thyrotoxicosis.

SUMMARY

Pathological function of the thyroid in mongoloids is a much discussed question. We had two girls under observation who demonstrated the two extreme possibilities in thyroid function. The one developed cretinism and was restored to a euthyroid state by

thyroid therapy. The typical cretinoid facies was changed under therapy to that of a characteristic mongoloid. The other was a typical mongoloid with a congenital heart malformation who developed an acute thyrotoxicosis in crisis and died. Her autopsy report is given in detail.

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We wish to express our appreciation for the cooperation of Dr. Elkin of Pondville Hospital, Massachusetts, for x-ray examinations; Dr. A. A. Luisada of Chicago Medical School for ECG; Dr. A. B. Russfield of Massachusetts General Hospital, Boston, for histological interpretation of the pituitary. We are also grateful for the assistance of our tissue technicians, Mrs. M. Friedmann and Mr. J. Martin; and to Mr. A. Barnes for the photographs.

INHIBITORS OF CARBONIC ANAHYDRASE IN PEDIATRIC THERAPY. S. Cutillo. (Pediatria, 65:32-45, Jan.-Feb. 1957.)

The author describes the changes of the plasma electrolytes caused by giving a preparation of acetazolamide in 12 children with different diseases caused by a disturbance of the electrolyte balance. The children were from 6 to 10 years old. The drug was given by mouth in a dosage of 5 to 10 mg. per kilogram of body weight per day for 4 consecutive days. Reduction of the alkaline reserve occurred in all children; in 4 it was so marked that the administration of acetazolamide had to be discontinued. Reduction of the total eletrolytes in the blood occurred in all children but was less marked in 2 children with nephrosis and in 2 with circulatory insufficiency. In 2 children with habitual vomiting who were being given rehydration therapy, the drug had a rapid normalizing effect on the hypochloremia and reduced the alkaline reserve.—*J.A.M.A.*

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

SOME POSSIBLE ETIOLOGICAL FACTORS IN THE RECURRENT VOMITING OF CHILDREN.*

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The etiological factors concerned in the recurrent vomiting of children have always been hidden in obscurity. As long ago as 1861, Lombard accurately described the clinical picture of the condition and outlined the treatment much as we follow it today. But to him as well as to all who have followed since, the causative agent has been a stumbling-block.

Many different views have been held by the writers who have so clearly described the symptomatology of recurrent vomiting and from the number of accumulated histories all have agreed upon certain points. They have agreed that an underlying neurotic constitution, inherited or acquired, is practically the rule, and that the exciting cause is often found in fright or excitement, great fatigue, anger, sudden exposure to cold and rarely to blows upon the abdomen, all of these believed to act upon or through the nervous system. The negative side is especially worthy of emphasis. They have agreed that the attacks are not directly attributable to errors in diet.

A decided advance was made when Edsall, Pierson and Marfan showed that in the attacks acetone, diacetic acid and β-oxybutyric acid are excreted in the urine in large amount.

Acquainted with these facts, two and a half years ago Dr. Richards and I began to study this question of the etiology of these attacks, making use of material which Dr. Holt most

*Read before the Eighteenth Annual Meeting of the American Pediatric Society held at Atlantic City, June 1, 1906.

Reprinted from ARCHIVES OF PEDIATRICS, 24:401-413, June 1907.

generously placed at our disposal. Three children suffering from these attacks have been constantly under observation since then and we have been exceedingly fortunate in having seen at least a dozen others. From a study of the urine of these cases we hoped to obtain an idea of the metabolic changes which accompany the attacks, in the belief that if this were possible we might be able, by suitable means, to reproduce the symptoms in experiments on animals.

In the first place, we have confirmed the often-repeated observation of the presence of acetone and diacetic acid. In some cases we have found β-oxybutyric acid to be present. The summary of our examination in this regard it is not necessary to give, since it is a mere confirmation of the work of others. It is sufficient to say that in the vast majority of cases of this type these substances are excreted in fairly large amounts in the urine. They are usually present before the attack of vomiting comes on, but in one case they were not found till after the vomiting had begun.

We have confirmed the observations of others in another respect, namely, that during and especially at the outset of an attack there is an increased excretion of uric acid. We find invariably a heavy sediment of amorphous urates, which fails to occur when the vomiting ceases. Relating to the excretion of sulphur, the excretion of sulphuric acid diminishes while that of the neutral sulphur, *i.e.*, unoxidized sulphur, increases.

In J. S., the only specimen we tested in this regard, lactic acid was observed to occur at the onset of the attack, and was not found after recovery had ensued.

Our results on indican excretion agree with those of other observers in showing that the quantity of indican is increased in a high degree before and in the first days of the attack. It may continue to be excreted in large amounts throughout the attack and may be detected in abnormal amounts even after recovery.

A brief consideration of the possible significance of these urinary changes will indicate the ground on which our experimental work was based.

It is now the general belief that fats yield energy to the body as the result of a series of oxidative transformations, the final products being CO_2 and H_2O. Under perfectly normal conditions this transformation is a complete one, *i.e.*, only CO_2 and H_2O are excreted and none of the intermediate products

appear in the excreta. Among these intermediate products of the combustion of fats are β-oxybutyric and diacetic acids.

The recent researches of Weintraud, Rosenfeld, Hirschfeld and others have shown, however, that the combustion of fats is not complete unless at the same time there is an adequate oxidation of carbohydrate. The processes by which fat is burned are so dependent on the simultaneous combustion of carbohydrate that, if for any reason carbohydrate fails to be burned in sufficient degree, the intermediate products of fat metabolism appear in the urine, *i.e.*, diacetic, β-oxybutyric acids and acetone. Carbohydrate may fail to be burned in sufficient amounts for either or both of two causes. It may not be present in sufficient quantity in the diet, or the body cells may have lost in a greater or less degree their power of oxidation of carbohydrate. For the former reason, the acetone bodies are excreted in starvation; for the latter reason, they make their appearance in diabetes.

If we should assume that this diminution in carbohydrate combustion is the *sole* cause for the elimination of acetone bodies in these cases of recurrent vomiting, then we must decide on what factor the limited carbohydrate combustion depends.

One consideration leads us to believe that it does not arise as a result of carbohydrate starvation, namely, that the interval of time in many cases which exists between an apparently normal condition of the child and the onset of vomiting with the appearance of these substances in the urine is no longer than elapses between two consecutive times of feeding. In such cases it is obivous that the factor of starvation cannot be the essential factor. It seems more logical to assume that it is mainly due to a diminished power of oxidation of the body cells.

In any case, in these attacks the acetone bodies are probably excreted as the result of lessened oxidation of fat, brought about either indirectly as the result of lessened sugar combustion, or by a direct influence of some unknown nature on fat combustion.

Uric acid is one representative in the urine of the metabolism of nuclear compounds. Its excretion may be markedly increased by the addition of nuclear substance or of nuclein derivatives to the diet. In these cases, however, its increase cannot be due to such a cause as this, for the composition of the diet is either unchanged or is very much diminished. It must arise, therefore, as a product of the decomposition of nucleoproteids of the body, *i.e.*, it is largely *endogenous* uric acid.

The nucleoproteids are decomposed in metabolism with the formation of:

Adenin	$C_5H_5N_5$
Guanin	$C_5H_5N_5O$
Hypoxanthin	$C_5H_4N_4O$
Xanthin	$C_5H_4N_4O_2$

The enzymes guanase and adenase transform guanin and adenin into xanthin and hypoxanthin respectively:

$$C_5H_5N_5O + H_2O = C_5H_4N_4O_2 + NH_3$$
$$C_5H_5N_5 + H_2O = C_5H_4N_4O + NH_3$$

Hypoxanthin and xanthin are then transformed into uric acid by oxidation brought about by the influence of an enzyme, oxidase:

$$C_5H_4N_4O + O_2 = C_5H_4N_4O_3$$
$$C_5H_4N_4O_2 + O = C_5H_4N_4O_3$$
Uric acid.

Not all, however, of the uric acid thus formed is eliminated as such. Under the influence of a *uricolytic* ferment, recently discovered, uric acid is further broken down by oxidation, so that in man only about one-half of the uric acid *formed* is eliminated in the urine as such.

To return to these cases, then, we cannot explain the increased elimination of this substance by change in the composition of the diet. It could, therefore, be due to an increased formation or to a decreased oxidation of uric acid. That it is due to decreased oxidation is suggested by the figures for total nitrogen.

In one case in which the uric acid estimations of the patient were made while the nitrogen values of the third and fourth days or the fourth and fifth are nearly constant, there is a very marked decrease in uric acid. If this decrease in uric acid, which, as other figures show, is a decrease toward the normal and doubtless has the same significance in a reversed sense as the initial increase in uric acid, were due to a lessened metabolic decomposition of nuclear compounds a decided change in the nitrogen elimination would probably accompany it. That is, at the same time that the purin bases are split off from the nucleoproteids, metabolism of the nitrogenous portion of the nucleoproteids takes place and increased elimination of nitrogen would result. Since the proportion of purin bodies which can be obtained from any single

nucleoproteid is small (1 per cent.) and since the amount of nitrogen is large (16 per cent.) it is obvious that an increase in uric acid (which represents increase in nuclein metabolism) must be accompanied by a far greater increase in total nitrogen. These considerations have led us to the conclusion that the origin of the increase in uric acid in these cases, not being due to change in diet, or to increased nuclein metabolism, must be due to decreased destruction. Since the destruction of uric acid takes place as a process of oxidation, we may conclude that oxidation of uric acid at the outset and in the first periods of the seizures we are studying, is interfered with.

Additional evidence of interference with oxidation is shown by the elimination of sulphur of the urine. Normally, about 90 per cent. of the total sulphur is excreted in the form of sulphuric acid, *i.e.*, oxidized sulphur. Most of the SO_3 arises from the oxidation of the sulphur-containing radicals in the proteid of the diet. Most of the unoxidized sulphur arises from the metabolism of the sulphur-containing proteids of the body cells. A decrease in the diet would, therefore, by lessening the SO_3 in a greater degree than the neutral sulphur, increase the ratio. For this reason it is found that the ratio of neutral sulphur to sulphuric acid sulphur in starvation increases. But it is equally obvious that in such a condition the total sulphur will diminish. In our cases, this is not found to be the case. The total sulphur of the two days analyzed remains the same, while the neutral sulphur rises and the oxidized sulphur falls. We believe this change to be due not to starvation, but to an interference with the processes by which sulphur is oxidized to SO_3.

Still further and more convincing than all is the observation of the occurrence of lactic acid. Lusk has shown very recently that in the combustion of dextrose, lactic acid is formed as an intermediate product. It had previously been shown that lactic acid introduced into the body is completely oxidized, *i.e.*, none of it reappears in the urine. In conditions of incomplete oxidation, however, lactic acid appears in the urine spontaneously and if injected is excreted as such. It is, therefore, a decidedly abnormal constituent of the urine and as much as any other constituent may be looked upon as an indication of decreased oxidation.

To sum up these conclusions, we believe that the figures we have quoted and the considerations which we have offered justify the belief that at the outset of the attacks there is an interference

with certain metabolic processes in which oxidation plays a part; that as the attack wears off the urinary signs of this interference wear off.

It has been stated that in the urines of these cases we have confirmed the observation that abnormally large amounts of indican are excreted before the attack. This indicates, of course, an increase of putrefactive processes in the intestine, with an increase not only of indol, but also of skatol, phenols, etc. We have given our reasons for the belief that at the same time there is a lessened power of oxidation in the body.

The question at once arose of the possibility of a relationship between these two factors. Urinary indican results as a synthetic product of the oxidation of indol. Indoxyl is converted into indican by combination with sulphuric acid. The same changes take place in the excretion of skatol, which is simply methyl indol. Indol and skatol then require oxidation before transformation into the final form in which we find them in the urine.

Phenol, however, combines directly with sulphuric acid, forming phenol-sulphuric acid. It has been argued by some competent observers that this power of the cells of effecting the combination is dependent upon simultaneous oxidation; that influences which diminish the power of oxidation lessen power of phenol synthesis.

Comparatively few data regarding the toxicity of indol and skatol exist. Large amounts (18 grams) have been administered to healthy animals with the production of no symptoms. The matter is summed up in Kunkel's Toxicologie with the statement that from the experimental evidence at our disposal we must conclude that indol is non-toxic. This indicates in a striking manner the adequacy of the organism for transforming substances of this type.

If, however, the ability of the organism to effect this oxidative transformation is diminished, it is possible that any toxicity which these substances possess will be exhibited. Our animal experiments are designed to throw some light on this question.

As means of diminishing oxidations we have made use of potassium cyanide and of chloroform. Potassium cyanide has been shown very definitely to dimnish the ability of cells to utilize oxygen even though oxygen may be present in normal amounts in the blood. Chloroform possesses the same property in a lesser degree.

In the first series of experiments on rats, guinea pigs and rabbits, the effects of definite doses of phenol and indol in normal animals were compared with those produced by the same doses in animals previously injected with small amounts of KCN or previously subjected to chloroform anesthesia.

From our experiments we conclude that diminution of oxidation intensifies and prolongs the poisonous effect of a moderate amount of either phenol or indol.

Our experiments on dogs afford a better idea of the nature of the effect which indol is capable of producing when its oxidation is interfered with. We have not yet extended our studies in dogs to phenols and skatol.

In the first place, we convinced ourselves that the quantities of indol (0.25-0.5 gram) which we used in combination with the other poisons (KCN and $CHCl^3$), given alone, produced no symptoms. If, however, a dog is poisoned by repeated small doses of potassium cyanide which are sufficient to produce distinct but not fatal symptoms of cyanide poisoning, both before and after the introduction of the indol, very marked symptoms result, which cannot be attributed to the action of the cyanide alone.

In the first experiment it was difficult to attribute any of the symptoms to the effect of the indol in the hours directly succeeding the injection. There was muscular twitching and evidence of increased peristalsis of the intestine, which may have been due to this substance. But, after ten to eighteen hours, effects were evident which were not due to the cyanide alone, and which we attribute to the action of indol, a condition of stupor and semiconsciousness came on which was interrupted by periods of wild delirium, marked by frantic, uncoördinated movements and shrill screaming. The delirium came on at times spontaneously, and always followed the stimulation of rough handling or rectal irritation produced by the insertion of a thermometer. This condition lasted till the death of the animal a week after the indol was given. During this period there was marked exaggeration of the reflexes, spasticity of the hind limbs, total blindness. During the whole period, food or water was not voluntarily taken; water given by a stomach tube was sometimes retained, though there were signs of nausea. Milk, diluted milk, or beaten egg, given in the same way, was immediately vomited. Throughout the whole period there were noticed in a marked degree the typical gurgling sounds of increased intestinal peristalsis, but no feces were passed.

Two other animals treated in the same way with a proportionally larger dose of indol developed identical symptoms and died on the third day.

In two dogs, a single injection of cyanide, accompanied with a smaller dose of indol, was given. One dog was killed after thirteen days, during which time the prominent symptoms were blindness, mental depression, with some delirium, increased reflex excitability, enormous appetite associated with increasing emaciation, constant nausea and bloody feces.

The second dog died after a period of five weeks, in which the blindness and nausea were the most prominent symptoms. During the three days preceding death, however, he developed the mental signs described above.

If, instead of potassium cyanide, prolonged anesthesia with chloroform or artificially induced asphyxia be used as means of reducing oxidation, strictly comparable results may be obtained. It should be mentioned that in the case of chloroform the gastrointestinal symptoms seemed to be more marked than with potassium cyanide. Not only did the feces contain blood, but bloody material was vomited.

An interesting fact has been noted with regard to the excretion of indican. The doses of indol which we have used will be entirely excreted by a normal animal in the form of indican in twenty-four hours. If at the same time its oxidation is diminished, the amount in the urine becomes less and its excretion is prolonged over a longer period of time (forty-eight hours or more). This emphasizes the important clinical fact that the amount of indican in the urine depends not only upon the amount of indol formed and absorbed, but also upon the capacity of the body cells to oxidize it.

At the autopsies of the animals which have been poisoned as we have described, the results are very uniform: Marked congestion of the gastrointestinal tract, especially of the duodenum, lower part of the ileum and colon with extensive necrosis of the mucosa and even of the submucosa. There is blood in the intestinal contents. The liver showed very great degenerative change, there was excessive cerebrospinal fluid and the tissue of the brain was soft. The more acute the poisoning the more marked were the changes in the gastrointestinal tract.

That the effects which we have described are due to the indol and that they are not due to the direct effect of the poisons which

we have combined with it we are convinced. In the first place, control experiments on potassium cyanide alone agree with the very extensive experience of Geppert and others, that when recovery from cyanide poisoning occurs at all it is rapid and complete, the only after effects being weakness from exhaustion. In the second place, we are able to produce the same symptoms with the second drug, chloroform, which bears no resemblance to potassium cyanide, save in its power to affect oxidations. Thirdly, we are able to produce the symptoms by mechanically reducing oxidation, *i.e.*, by asphyxia.

It is apparent, then, that the symptoms of this form of indol poisoning may be divided into two groups, nervous and gastrointestinal. We made one experiment designed to afford an explanation of the gastrointestinal disturbance.

In one dog a section of the small intestine, 8 to 10 inches long, was severed from the main gut, its ends sewed to the abdominal wall, and an end to end anastomosis of the main gut established. A month later, when recovery was complete, the dog was poisoned with KCN and indol in the manner previously described. The urine gave no reaction for indol, but it could be detected in washings of this isolated loop of intestine. Furthermore, the odor of indol could be detected at the abdominal opening of the fistula.

This experiment indicates that if indol is circulating free in the blood, owing either to abnormally great formation or to abnormally decreased oxidation, it is excreted by the intestine rather than by the kidney.

We have proof that when the power of oxidation is diminished, indol, ordinarily non-toxic, is a most powerful poison. It is a matter of observation that children subject to attacks of recurrent vomiting exhibit evidences of increased intestinal putrefaction by an increase in the urinary indican whose precursor is indol, and often by foul stools. During the attack, constipation is the rule, which would still more increase the absorption of indol. The presence of indol in comparatively large amounts can, therefore, be assumed, and we have shown that during these attacks diminished oxidation is present.

We have evidence that the toxicity of phenol is increased, but have not sufficiently studied this nor skatol and the cresols. Since the transformations that these undergo in the organism are the same as indol and phenol, there is every reason to believe that the results will be similar. Let it be understood, however, that we do

not claim that these aromatic substances are alone the cause of these attacks. It is possible that other substances, absorbed from the intestinal canal or formed in intermediary metabolism, may be also responsible.

We have not produced in animals symptoms identical to those in children and probably shall not be able to do so. The diminished oxidation in children is moderate but prolonged. Our imperfect methods allow us to produce an intense, but evanescent, diminution of oxidation in animals. As soon as this wears off, the poisons are rapidly eliminated by the kidneys; before it wears off, it is probable from the experiments previously mentioned, that the gastrointestinal tract attempts to get rid of them. This would seem to account for the gastric symptoms. It is only while under the influence of the poisons that there is diminished oxidation and the poisoning is so profound that the animals are practically anesthetized. While this was wearing off they did show gastrointestinal symptoms, vomiting, sometimes bloody, nausea and bloody stools. In children, with the moderate but prolonged diminution of oxidation, gastric symptoms can readily occur, and we have reason to believe that these substances are eliminated by the stomach, from the examination of the vomitus of F. Two samples of vomitus, clear and not bile-stained, contained a trace of indol.

These aromatic substances, as the experiments show, in large enough amounts are convulsants, and it is suggestive to read that one of Snow's patients up to the age of five years always had a convulsion before each attack and that Langmead's fatal case terminated in convulsions.

To compare the autopsy findings is unsatisfactory for the reason that few postmortem examinations on children dying from recurrent vomiting have been recorded, and those in a most meagre way. Griffith found necrotic changes in the stomach and intestines. Marcy's case was carefully examined. The stomach showed extravasated blood under the mucosa with apparent softening; this was also marked throughout the intestines. Microscopically he found almost complete necrosis of the entire mucous membrane of both the stomach and intestines. Most of the epithelial cells did not stain at all, they being represented by an indistinct granular mass; the necrosis appeared to have invaded the submucous coat. There was fatty infiltration of the liver and slight parenchymatous degeneration of the pancreas, spleen and kidney.

As mentioned above, our dogs showed very great congestion of the gastrointestinal tract with extravasations of blood. In places the mucous membrane was very necrotic and there was enormous degeneration of the liver.

It appears to us in the light of our present knowledge that a shock, excitement, fright, anger or something of the kind, is exerted upon an unstable nervous system, unstable by inheritance or development, and also by age; for we cannot doubt that similar shocks are felt at a later time, but in the course of growth the brain and nervous system acquire a more stable equilibrium. As a result of this, in some way or other, unknown to us, a diminished power of oxidation results and the organism loses the power to detoxify substances absorbed from the intestine which have been present there in excess; these circulate in the blood, exerting their poisonous action and cannot be excreted by the kidneys because they are not brought to them in the proper form. It seems probable that they are excreted and reabsorbed by the stomach and intestine, in the light of which vomiting would appear to be eliminative and thus a protective mechanism.

Finally, the power to oxidize and detoxify these substances returns; they are rapidly eliminated, and quick improvement results.

STREPTOCOCCI AND INFECTIOUS NEPHRITIS. R. Wahl. (Press méd., 63:1366-1368, Oct. 15, 1955).

Acute nephritides, including the one associated with scarlet fever, are usually a consequence of infection of the upper respiratory tract with a group A beta-hemoyltic streptococcus. The incidence of these nephritides varies widely according to locality, season, and year but is not correlated with the incidence of streptococci infection in general or that of other complications, such as acute articular rheumatism. Sometimes veritable epidemics of nephritis occur. These unexpected variations are explained by the fact that, of the 40 types of streptococci in group A, there is one, type 12, that is peculiarly nephritogenic. Certain other types probably also play a role. The usual lack of relapses in connection with the disease is explained by the particular form of immunity, i.e., an immunity to the type, conferred by the infections with group A streptococci. Type 12 infections should be treated intensively and as early as possible, so that nephritis may be prevented.

—J.A.M.A.

DEPARTMENT OF ABSTRACTS

Conducted by
MICHAEL A. BRESCIA, M.D., NEW YORK

BLACKBURN, E. K.: THE BREATH IN ACUTE LEUKEMIA. (British Medical Journal, 5011:146, Jan. 19, 1957).

A physical sign is described consisting of a peculiar sweet odor of the breath found in relation to seventy-three cases of leukemia (fifty-one acute, twenty-two chronic). It was present in twelve cases of acute leukemia without obvious clinical involvement of the gums, mouth, or upper respiratory and alimentary tracts. In six of these cases there were signs and symptoms, such as splenomegaly, to suggest the true diagnosis, while ordinary clinical examination of the other six cases, halitosis apart, was unrewarding, and it was only after examination of the blood and bone marrow that a firm diagnosis could be made. Possible sources of the halitosis are discussed. AUTHOR'S SUMMARY.

IMPERATO, C. and LANDUCCI, L.: ELECTROENCEPHALOGRAPHIC STUDIES OF CEREBRAL TRAUMA OF LABOR. (Il Lattante, 28:1, Jan. 1957).

The authors report their findings on twenty-two newborns who suffered brain injury at birth. The E.E.G.'s were done from 2 days to 41 months of age in cases weighing at birth 1.8 kg. to 4.3 kg. The earliest recording was done 37 hours after birth. Fifteen cases were done during the first month and all cases had a history of convulsions. The E.E.G. findings fall into three types. The first group, including nine cases, presented definite epileptic activity. This activity was present during a convulsive attack (5 cases) as well as during the interseizure period. The second group were characterized by bursts of slow activity, irregular and wide, which appear paroxysmally in a flat record (5 cases). The earliest observation of this type occurred in an 11-day-old child. The third group was characterized by the appearance of continuous or prolonged discharges of fast activity (5 cases) and obviously independent of drowsiness or sedation. The authors feel that the electroencephalogram should be used more often in the newborn suspected of brain injury to better evaluate the presence of such injury, and possibly, the extent of such injury. M.A.B.

FIELDS, E. M.: TREATMENT OF METABOLIC INSUFFICIENCY AND HYPOTHYROIDISM WITH SODIUM LIOTHYRONINE. PRELIMINARY REPORT. (Journal American Medical Association, 163:817, March 9, 1957).

A study was conducted on one hundred children to determine the clinical effects of a new thyroid-like hormone, sodium liothyronine (L-triiodothyronine), in treating metabolic and hypothyroid disorders. The patients in this study ranged from 1 to 18 years of age. Forty of the patients were given a diagnosis of metabolic insufficiency; the other sixty of hypothyroidism. All children in both groups had been treated previously with thyroid extract, thyroglobulin, and thyroxin. The average dose of liothyronine varied from an initial dose of 5 mcg. daily to a maximum of 50 mcg. daily, with a mean dose of 15 to 25 mcg. given daily for three weeks of each month in this three-month trial. The forty patients with metabolic insufficiency showed the following responses to liothyronine: 22, excellent; 15, good; 3, fair. The sixty patients with hypothyroidism showed the following responses: 35, excellent; 22, good; 2, fair; and 1, poor. In both groups of children, liothyronine brought about rapid clinical improvement, particularly in those children whose conditions were refractory to standard thyroid preparations. It is concluded that administration of liothyronine is an effective, safe, and well-tolerated form of treatment for metabolic insufficiency and hypothyroidism in children. Further studies of this compound seem warranted and are recommended.

AUTHOR'S SUMMARY.

THANAWALLA, J. K.: TYPHOID FEVER IN CHILDREN. (Indian Journal of Pediatrics, 23:421, Dec. 1956).

Observations have been made in 189 cases of typhoid fever in children. The case fatality rate was 6.9 per cent and excluding moribund cases 3.7 per cent. Typhoid fever was more common in the age group of 6 years to 10 years. The mortality rate was higher amongst male children. In Bombay, the incidence of typhoid is higher in the months of May and October. Relative bradycardia observed in adults was generally absent in children. The typical typhoid tongue was observed only in very toxic cases and in older children. Though the incidence of complications is more in children than in adults, the case fatality rate is less in children

than in adults, except in complications due to diarrhea and circulatory failure. The relapse rate was 5.2 per cent with no fatality in this group. Chloramphenicol when administered as a powder gave better results than the liquid. AUTHOR'S SUMMARY.

LEWIS, A. J.; PADER, E. and ELSTER, S. K.: THE EFFECT OF SALICYLATES AND ADRENOCORTICAL HORMONES ON C-REACTIVE PROTEIN. (American Journal Medical Sciences, 233:309, March 1957).

The blood of eight patients with malignant neoplasms was studied and was found to contain C-reactive protein in moderate amounts. Acetylsalicylic acid, cortisone, prednisone and adrenocorticotropin-gel were administered to these patients and the level of C-protein studied. In no case was the amount of C-reactive protein reduced. These studies suggest there is no direct effect of these drugs upon the metabolism of C-reactive protein. It is inferred that the disappearance of C-reactive protein from the blood of patients with acute rheumatic fever treated with salicylates or adrenocortical hormones is due to suppression of the inflammatory process, rather than to a nonspecific effect on the protein itself.
AUTHORS' SUMMARY.

ADELSON, H. T.: LONG-TERM DICUMAROL ADMINISTRATION AS A THERAPEUTIC TRIAL IN SICKLEMIA. REPORT OF A CASE. (New England Journal of Medicine, 256:353, Feb. 21, 1957).

A trial course of long-term anticoagulant therapy in a case of sickle cell anemia is reported. The apparently beneficial and encouraging results are described. It is suggested that this therapeutic approach justifies further trial and evaluation.
AUTHOR'S SUMMARY.

RECCHIA, F. and RAVAZZONI, L.: CEREBROSPINAL FLUID FINDINGS IN DIPHTHERITIC PARALYSIS. (Aggiornamenti Sulle Malattie Da Infezione, 2:373, Nov.-Dec. 1956).

In twenty-one children with both late and early diphtheritic paralysis, an increase in pressure, protein and nitrogen was found in the spinal fluids. These findings did not seem to have any prognostic value. However, as the paralysis improved the protein of the spinal fluid tended to become normal. M.A.B.

ASUNG, C. L.; CHARCOWA, A. I. and VILLA, A. P.: A STUDY OF THE NONHYPHOTIC CALMATIVE EFFECT OF 2-ETHYLCROTONYLUREA (NOSTYN) IN CHILDREN WITH BEHAVIOR PROBLEMS. (New York State Journal of Medicine, 57:1911, June 1, 1957).

A new calmative drug, Nostyn, was studied for its effect on the hyperexcitable, uncooperative, or antisocial behavior patterns of fifty-one children, 2 to 12 years of age, carefully selected because of difficulty in managing them in a large hospital pediatric service. The drug was administered to all children in one-half the average adult dosage and was found to be highly effective in normalizing the disturbed behavior in thirty-five cases (68.6 percent), of minimal or questionable value in eight (15.8 percent) and of no value in four (7.8 percent). The drug affected the behavior adversely in the remaining four cases. Of six patients with histories of enuresis, two stopped bedwitting, and four improved markedly while on the drug. However, one child who was not previously enuretic commenced bedwetting when the drug was given.

Nostyn appeared to have a calmative but not hypnotic action in the dosages employed. No toxic side-effects were noted, with particular attention being paid to the hematopoietic system. Nostyn merits continued study as a potentially useful, new adjunct to the correction of certain common behavioristic problems including enuresis in children. AUTHORS' SUMMARY.

VICTOR A. B. and IMPERIALE, L. E.: THE PULMONARY AND SMALL BONE CHANGES IN INFANTS WITH SICKLE CELL ANEMIA. (New York State Journal of Medicine, 57:1403, April 15, 1957).

Two infants are presented who demonstrate the changes in the lungs and small bones of the hand that can occur with sickle cell anemia. Emphasis is placed on the roentgenographic findings which include pulmonary infiltrations possibly with small micronodules and marked destruction of short bones. An attempt is made to correlate these findings with pathologic anatomy. These cases are presented in order to add to the very small body of literature on this subject and thus again remind physicians that sickle cell anemia has protean manifestations and should be part of the differential diagnosis in tuberculosis, pneumonia and acute osteomyelitis. The first patient, who is still living at the time of this writing, is on prophylactic oral penicillin in an attempt to determine

whether the frequency of recurrent infection cannot be diminished. The early death of the second case raises the question of the prognostic significance of the above described changes in infants with sickle cell anemia. More pathologic bone and lung studies are needed to help explain this often baffling clinical picture.

AUTHORS' SUMMARY.

FOWLER, M.: BRAIN DAMAGE AFTER FEBRILE CONVULSIONS. (Archives of Disease in Childhood, 32:67, April 1957).

Five children, aged up to 2 years and previously normal, suffered from a prolonged convulsion at the beginning of a febrile illness. The patients remained unconscious after the convulsions, which lasted from 1 hour to 6 hours, developed spastic paralyses, and in four cases death occurred 4 days, 12 days, 4 weeks and 18 weeks respectively from the onset of the convulsion. Pathological examination revealed neuronal necrosis of variable distribution and severity in the cerebral cortex, basal ganglia and cerebellum with no evidence of the direct action of microorganisms. The changes are considered to be the result of systemic anoxia of convulsive origin, or, less likely, to be due to a specific mechanism acting locally in the brain. The importance of convulsive cerebral degeneration as a precursor of epilepsy and as the cause of infantile spastic and behavior disorders is mentioned. M.A.B.

DOLL, R. and HILL, A. B.: DEATHS FROM POLIOMYELITIS AMONG BRITISH DOCTORS. (British Medical Journal, 5015:372, Feb. 16, 1957).

The evidence given here suggests that men between the ages of 25 and 45, who are practicing medicine in Great Britain, are at special risk of dying of poliomyelitis. The actual number of deaths recorded (8) is small in relation to the number of men at risk (nearly 35,000), but at the rate of the general population, not more than one death would have been expected to occur.

AUTHOR'S SUMMARY.

EPSTEIN, B. S.: SUBCUTANEOUS UROGRAPHY IN INFANTS. (Journal American Medical Association, 164:39, May 4, 1957).

Subcutaneous urography with a 50 per cent solution of diatrizo-

ate (Hypaque) sodium diluted to 25 per cent is advantageous in infants. The usual dose for children up to about 16 months is 15 cc. diluted to 30 cc., with 15 cc. injected parascapularly on either side. The injections may be given quickly and with little discomfort to the patient. Twenty-three of twenty-five films obtained were satisfactory, while the remaining two were of sufficient clarity to permit diagnosis of a normal urinary tract.

AUTHORS' SUMMARY.

MYASTHENIA GRAVIS: DIAGNOSIS OF ATYPICAL FORMS. E. Stiefel. (Rev. clin. espan., 56:265-268, Feb. 28, 1955). Myasthenia gravis is a progressive nonhereditary disease that affects the muscles of the face, lips, tongue, throat, and neck. It is more frequent in women than in men. The author reports two cases, one in a man, who showed typical symptoms and reacted favorable to prostigmine. The treatment caused improvement of his working capacity that was still maintained one year after treatment was started. The other patient, a 22-year-old woman, had an atypical form of the disease. Her nuchal and masseter muscles were especially affected. She was unable to maintain her head in the erect position and mastication was very difficult. The first attack occurred when she was 15 years old. Three subsequent attacks have occurred, each being more acute than the previous one. In all four attacks prostigmine gave no relief. An electrodiagnosis of the affected muscles was not made. Roentgenograms of the thorax did not show an enlarged thymus. Roentgen therapy over the thymus region gave no relief. A biopsy specimen showed the typical histopathological changes of myasthenia gravis, consisting of almost complete loss of transverse striations of muscle fibers, multiplication of the nuclei, fatty degeneration of the sarcolemma, and massive lymphocytic infiltration on the edges of the muscle fibers. An intense treatment with intravenous injections of vitamin B_6 for a month produced marked improvement consisting of disappearance of fatigability and return of muscular power to the affected muscles. The patient became able to maintain her head either erect or at any posture, and her mastication became normal.—*J.A.M.A.*

BOOK REVIEWS

Conducted by
MICHAEL A. BRESCIA, M.D., NEW YORK

THE RIDDLE OF STUTTERING. By C. S. Bluemel, M.D. Cloth. Pp. 142. Price $3.50. Danville, Ill.: The Interstate Publishing Company.

This book, as its name implies, has undertaken to probe the age-old riddle of stuttering, and perhaps bring it closer to solution. From Hippocrates' and Aristotle's time to the present day, there has been much speculation as to the cause and cure of this baffling speech disorder. Medical science has contributed little to the cure and understanding of stammering. However, the field of psychiatry may yet contribute to the solution of this speech problem according to Dr. Bluemel, although it has come up with some rather sterile and conflicting interpretations. The concept that stammering is a "psychoneurotic disorder" rather than an impediment of speech has been quite widely accepted in the last two decades. Theories dating back to the nineteenth and even the eighteenth century point to the fact that stammering was associated with emotional disturbance; it is only lately that the stammerer as a person is considered in the speech disorder. The author differentiates between non-organized and disorganized speech. Non-organized speech or stuttering is the imperfect or non-fluent speech which occurs during childhood, when speech is in the making. He describes disorganized speech as stammering, or speech in the "unmaking". Poorly organized speech is readily disorganized and the personality of the stammerer may be considered to be disorganized as well. A great part of the book is devoted to the personality dynamics of the stammerer; his diffidences, self-consciousness, and tension. Because of his lack of awareness of his difficulties, speech phobia develops with eventual "mutism" and "spasm". The stammerer's predicament is further accentuated by the fact that he cannot hide his psychoneurotic reactions since they can be both seen and heard. Breathing, vocalization, and articulation become disturbed and he developes speech "aversion and avoidance". A secondary stage of stammering now comes into play, and is like other psychoneurotic disorders, such as nervous indigestion, tremor, or palpitation. Dr. Bluemel describes the principles of therapy in great detail. Speech training, he claims, should be centered in the

sensory rather than in the motor areas. Then attention should be directed to verbal thinking processes. Group therapy, rather than individual therapy is considered more advantageous because of greater objectivity and incentive.

Since this book deals largely with therapy of a sound, practical, and workable nature, it would be a valuable adjunct to the library of every psychologist, psychiatrist and speech therapist. The pediatrician, who is interested in disordered speech and its relationship to the stammerer as a "person", also will find this book most interesting and helpful. ELEANOR ROTHENBERG, M.A.

TREATMENT OF THE CHILD IN EMOTIONAL CONFLICT. By Hyman S. Lippman, M.D. Cloth. Pp. 298. Price $6.00. New York: McGraw-Hill Book Company, Inc., 1956.

This book is of value to those who deal with children and undoubtedly encounter many psychologic and psychiatric problems. The book is made more palatable by the author's frequent use of clinical material in his text. The care of behavior problems of children is an immense field with, as the author mentions, insufficient trained personnel to handle these problems. Because of this paucity of personnel, the author feels quite safe in placing the treatment of these problems in the hands of social workers, psychologists, "therapists" and psychiatrists but is wary of the physician and thus, his "psychiatric team" consists of the caseworker, the clinical psychologist, the child psychiatrist as well as the group therapist. This team is unbalanced since no mention is made of a pediatrician, who certainly should be a key man on any such team.

The author leans heavily on Freud and sexual matters seem to be over emphasized. In presenting a case of obsessional neurosis in a boy of ten years of age the author himself raises the question with regard to therapy treatment of this same boy, whether it changed his obsession from a disabling neurosis to a more easily tolerated character disturbance. Follow-up studies of children suffering from established obsessionsal neurotic illness will help to determine the later course this illness takes and the affect of different forms of therapy.

The chapter on the problem of prevention is well taken. The author recommends that "all persons whose work brings them in direct contact with children, recreation directors, workers in character-building agencies, clergymen, camp counselors, should

have the opportunity to attend seminars in the recognition of emotional problems in children". With regard to the teacher, who is in contact with the child probably more than any person including parents. "Every physically or emotionally sick teacher may have a destructive effect on the children she teaches, and though this may not affect the stronger, more secure children in her classes, it can harm the insecure conflicted ones. Often physically and emotionally sick teachers remain at work longer than is good for them or their pupils". The canard that the parents are always at fault is dispelled by the author.

MICHAEL A. BRESCIA, M.D.

MEDICAL SERVICES FOR RURAL AREAS. By William A. Mussie. Paper. Price $1.25. Cambridge, Mass.: Harvard University Press, 1957.

There are many rural areas that are medically poor such as summarized in this booklet. However, organized medicine has a moral obligation to extend good medical care to all peoples within the State.

The Tennessee Medical Foundation took steps to assist several rural areas in raising their substandard medical services.

One small city had been helped in developing a 44 bed hospital, another area established a modern drug store and a registered pharmacist. The Foundation helped establish a doctor's office with a general practitioner in a much deprived medical area.

The Tennessee Plan will set a persuasive pattern which other state medical associations may follow. To the medical profession on a national and state level it affords an ideal means of providing high grade medical service at reasonable cost to a large proportion of people. In public health it may provide means for extending services to areas where the prevention of disease will be the greatest.

The Foundation was notably worthy in curbing costly errors, planned programs to fit long range needs, and developed services best suited to that particular community's health requirements and economic resources. Most important of all they taught people to work together for their common good.

This is an invaluable study on Team Work and Team Leadership and may readily be applied in urban and rural areas within the nation.

It is a short, well written study with a challenge to other medically indigent areas in the nation. ELSIE MECHTA, R. N.

SERVICES FOR CHILDREN WITH HEARING IMPAIRMENTS. By The American Public Health Association. Paper. 1956.

This is a practical guide prepared by the Committee on Child Health of the American Public Health Association on establishing community programs for the hard-of-hearing children. The services included covers a wide range of professional interests. More recently, a survey disclosed that a third of our school population have had hearing screen tests. Better health coverage is necessary to make it 100 per cent. There are still many communities that lack hearing clinics, speech therapy and audiology centers. Greater interest should be taken by local communities to develop programs on hearing services. There still exists an inadequate number of otologists, audiologists and special teachers, but with adequate guidance local personnel may develop suitable programs to meet their needs, even on a regional basis. This guide is a challenge to teachers, pediatricians, speech therapists, otologists, and public health nurses everywhere to help promote programs on hearing conservation and rehabilitation. It is easy to read. The concepts and facts about hearing impairment are well defined and clearly express the needs of children with hearing impairment. It should appeal to persons whose decisions determine the operation of community services to children. ELSIE MECHTA, R. N.

TUBERCULOUS MENINGITIS IN INFANTS: CLINICAL FORMS AND THERAPY. L. Auricchio. (Arch. tisiol., 11:897-905, Dec. 1956).

In the past 6 years the author has treated 68 infants who had tuberculous meningitis: 23 with streptomycin, 16 with streptomycin and aminosalicylic acid, and 29 with streptomycin and isoniazid. Six children, 1 from the first group and 5 from the third, recovered. All the others either died in the hospital or were sent home in poor condition. Roentgenologic examination showed primary tuberculous complexes or adenopathies in 40 infants, caseus bronchopneumonia in 8, nodular disseminations in 15, and miliary dissemination in 5. Early diagnosis, immediate removal of the subject from the source of infection, and immediate treatment are necessary for recovery. Isoniazid, given in doses of 10 to 20 mg. per kilogram of body weight per day, has a good effect, especially if combined with glutamine therapy, which eliminates some of the toxic effect of isoniazid.—*J.A.M.A.*

ITEMS

A Fatal Case of Poliomyelitis in a Newborn Infant Delivered by Cesarean Section Following Maternal Death Due to Poliomyelitis. (Pediatrics, 14:235-237, Sept. 1954). A living male infant was delivered by Cesarean Section within five minutes after maternal death from undiagnosed poliomyelitis. Gestation had lasted 34 weeks, and the mother's fulminating illness had had its onset 24 hours prior to admission to hospital. The baby first showed signs of poliomyelitis at the age of 10 days; he died at 12 days. Type 1 (Brunhilde) strain of poliomyelitis virus was isolated from both the infant's and mother's spinal cord with the tissue culture technique. The disease processes seen at autopsy in the baby seemed to be of longer duration than those found in examination of the mother's tissues. Although positive proof is not forthcoming, this case and four cases in the literature, in which poliomyelitis developed after delivery by section, point strongly to the occurrence of transplacental passage of the poliomyelitis virus. In the instances of delivery by section at the time of maternal death this may be an agonal phenomenon. —*J.A.M.A.*

Pseudomonas Pyocyanea Meningitis Successfully Treated with Polymyxin. (Lancet, 1:759:761, April 10, 1954). Trapnell presents the case of a boy, aged 5½ years, who was admitted to hospital for reexploration of a cervical cord ependymoblastoma after a course of deep x-ray therapy. Eight days after operation, a small cerebrospinal fluid fistula developed at the upper end of the incision, which closed within two days. Two days later meningitis was diagnosed. The causal organism, Pseudomonas pyocyanea, was resistant to sulfonamides, penicillin, chlortetracycline (Aureomycin), oxytetracycline, and chloramphenicol, but sensitive to polymyxin B. Recovery followed a long course of intrathecal and intramuscular administration of polymyxin B. Previously unrecorded toxic effects of polymyxin therapy were observed in this case, namely, severe eosinophilia and xanthochromia of the cerebrospinal fluid. Other toxic effects observed were nausea and malaise, pain at the injection site, pain down the legs and in the back following intrathecal injections, and sacral edema. These effects disappeared in spite of continued polymyxin therapy. Transient mild albuminuria with cylindruria was also present.—*J A.M.A.*

AS THEY FIND IT–

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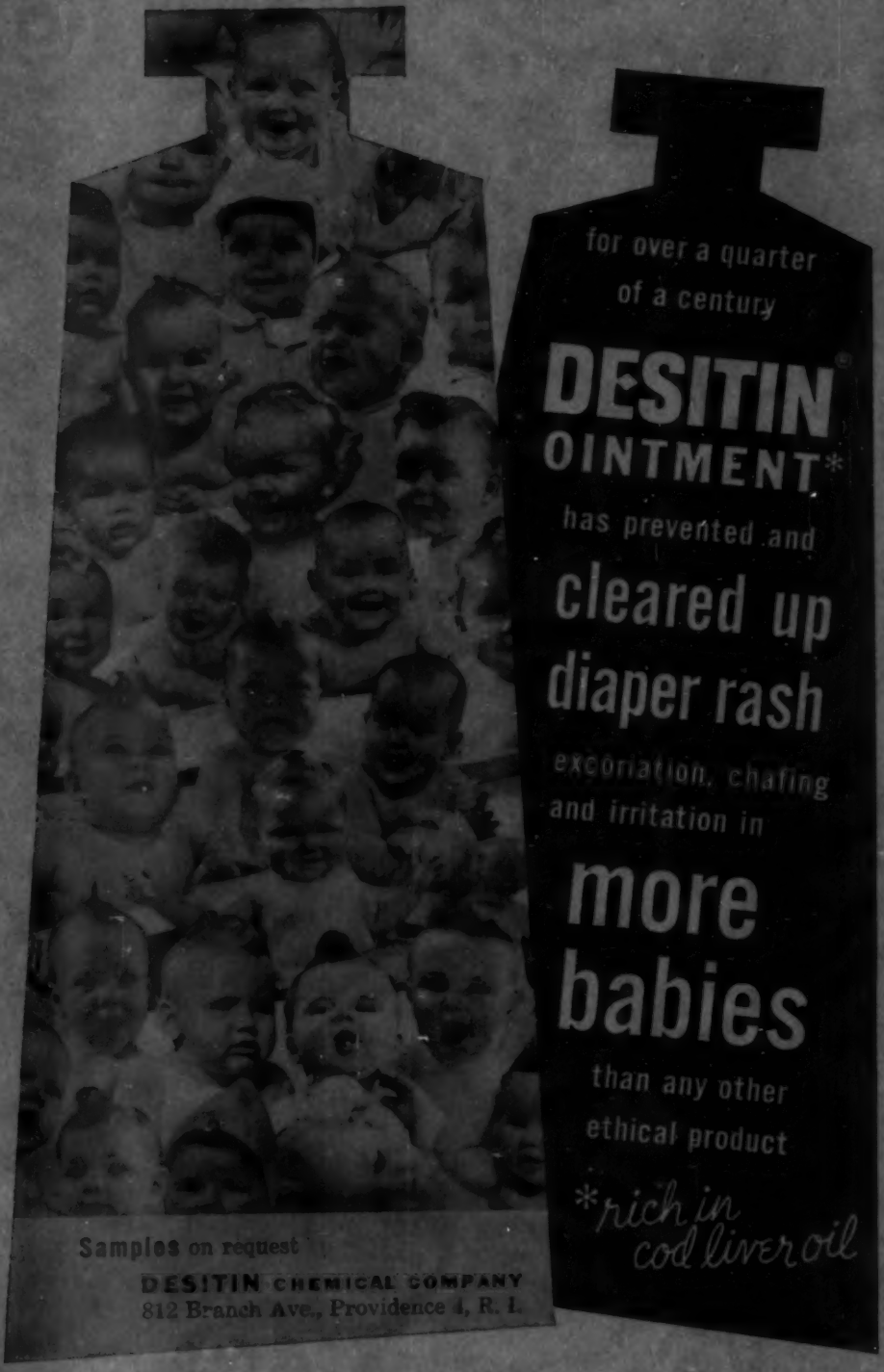
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